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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,339	01/03/2006	Barrie Bode	60004310-0022	8839

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EXAMINER

PITRAK, JENNIFER S

ART UNIT	PAPER NUMBER
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1635

MAIL DATE	DELIVERY MODE
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10/10/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/563,339	Applicant(s) BODE, BARRIE	
	Examiner JENNIFER PITRAK	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 9, 10, 12, 14-22, 24 and 26-29 is/are pending in the application.
- 4a) Of the above claim(s) 16, 26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9, 10, 12, 14, 15, 17-22, 24, 28, and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1635

DETAILED ACTION

Remarks

Applicant's amendments and arguments filed 07/03/2008 have been entered and considered. Claims 1-7, 9, 10, 12, 14-17, 19-22, 24, and 26-29 are pending. In the 07/03/2008 amendments, Applicant amended claims 1, 3-7, 9, 10, 12, 14, 15, 17, 19, 20, 22, and 24, canceled claims 8, 11, 13, 18, 23, and 25, and added claims 28 and 29. Claims 16, 26, and 27 are withdrawn as being directed to non-elected inventions. Claims 1-7, 9, 10, 12, 14, 15, 17, 19-22, 24, 28, and 29 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

In the prior Office Action, all claims were afforded the priority date of the instant application, which is 06/30/2004, based on the lack of support for SEQ ID NO: 3 in the provisional application, 60/484728, filed 07/03/2003. The priority of the claims is clarified herein.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

Art Unit: 1635

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/484,728, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application 60/484,728 does not contain the instantly claimed SEQ ID NO: 3. **Therefore, claims 12, 14, 17, 19, and 29 are granted priority to the filing date of the instant application, 06/30/2004. Claims 1-7, 9, 10, 15, 20-22, 24, and 28 are afforded the priority date of the provisional application, 60/484728, which is 07/03/2003.**

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections - withdrawn

The amendments to the claims have obviated the objections to claims 8, 11, 13, 20, 22, and 23 presented in the prior Office Action.

Claim Rejections - 35 USC § 102 - maintained

Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kilberg, *et al.* (1980, JBC, v.255:40119-9) as evidenced by Han, *et al.* (1999, U.S. Patent 5,891,864). This rejection is maintained for the reasons of record.

The claims are to a method of inducing apoptosis in a hepatocarcinoma cell by contacting the cell with an effective amount of an inhibitor of the ASC glutamine transport system.

Kilberg, *et al.* teach the inhibition of the ASC glutamine uptake system in Ehrlich cells, which are hepatocarcinoma cells (see lines 11-14, column 3 of Han, *et al.*), by contacting the cells with a series of glutamine uptake inhibitors (Table IV on p.4014 and first paragraph p.4014). Kilberg, *et al.* perform the instantly claimed step of contacting a hepatocarcinoma cell with an effective inhibitor of the ASC system. Absent evidence to the contrary, Kilberg's contacting a hepatocarcinoma cell with an ASC inhibitor would inherently result in the induction of apoptosis. Thus, Kilberg, *et al.* clearly anticipate the instant claims 1-3 and 6.

Response to arguments

Applicant argues that because neither the Kilberg reference nor the Han reference teaches or suggests inducing apoptosis, the claims are not anticipated. This is not persuasive because the Kilberg reference teaches the instantly claimed method step of contacting a cell with an effective amount of an ASC inhibitor. Absent evidence to the contrary, such a method step would inherently result in the induction of apoptosis. Applicant is referred to MPEP 2112 (II) ("Inherent Feature Need Not be Recognized at the Time of the Invention") for an explanation of anticipation based on inherency.

Art Unit: 1635

Claims 1-3, 5, and 6 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bode, *et al.*, (1998, Surgery, v.124:260-8, of record). This rejection is maintained for the reasons of record.

The claims are to a method of inducing apoptosis of a hepatocarcinoma cell (including SK-Hep cells) comprising the step of contacting the cell with an effective amount of an inhibitor of the ASC glutamine transport system.

Bode, *et al.*, teach treatment of SK-Hep cells with PMA (phorbol 12-myristate 13-acetate) (Figure 6 and p.264, last paragraph). PMA inhibits glutamine transport via ATB0 as taught by Bode, *et al.* at p.262, first paragraph under Results, which reads, "This phorbol ester-induced reduction in System B0-mediated glutamine transport activity was dependent on the concentration of PMA..." Absent evidence to the contrary, such a method step would inherently result in the induction of apoptosis. Thus, Bode, *et al.*, clearly anticipate each of claims 1-3, 5, and 6.

Response to arguments

Applicant argues that because the Bode reference does not teach or suggest inducing apoptosis, the claims are not anticipated. This is not persuasive because the Bode reference teaches the instantly claimed method step of contacting a cell with an effective amount of an ASC inhibitor. Absent evidence to the contrary, such a method step would inherently result in the induction of apoptosis. Applicant is referred to MPEP 112 (II) ("Inherent Feature Need Not be Recognized at the Time of the Invention") for an explanation of anticipation based on inherency.

Claim Rejections - 35 USC § 103 - maintained

Claims 1-6 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bode, *et al.* (1998, Surgery, v.124:260-8, of record). This rejection is maintained for the reasons of record.

The claims are to a method of inducing apoptosis of a hepatocarcinoma cell comprising contacting a cell with an agent that inhibits the uptake of glutamine by the cell, and wherein the cell is comprised by a patient. The phrase, "comprised by a patient" is interpreted as meaning "comprised in a patient."

Bode, *et al.*, teach the inhibition of ATB0 by contacting SK-Hep cells with PMA (described above, in the 35 USC § 102(b) rejection). Bode, *et al.*, do not teach a method wherein the contacted cells are in a patient. However, it would have been obvious to use an agent to contact cells in a patient because at the last sentence on p.266, Bode, *et al.*, suggest the use of ATB0 (transporter) inhibitors in patients by saying "[A]lthough this transporter is also expressed in normal human tissues, the hope is that tumor-specific differences in its regulation can ultimately be exploited in the development of new therapies for HCC." Although Bode, *et al.*, do not specifically teach that inhibition of ATB0 activity induces apoptosis, because the authors teach the step recited in the instant claims, this step is considered to have the effect of inducing apoptosis, absent evidence to the contrary. Thus, claims 1-6 and 24 would have been obvious at the time of the instant application.

Response to arguments

Applicant argues that because Bode, *et al.* do not teach induction of apoptosis and that only by hindsight is the conclusion of obviousness reached. This is not persuasive because Bode, *et al.*

Art Unit: 1635

teach all of the claimed method steps. The induction of apoptosis would inherently result from such steps, absent evidence to the contrary. As noted above, the induction of apoptosis is considered an inherent feature of inhibiting ATB0. The burden is on Applicant to show that the claimed anticipated or obvious method steps would not result in the claimed effect, in this case, apoptosis.

Claims 12, 14, 17, 19, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bode, *et al.* as applied to claims 1-6 and 24 above, and further in view of Khvorova, *et al.* (US 2007/0031844, filed as U.S. Provisional Application 60/502,050 on 09/10/2003). This rejection is maintained for the reasons of record.

The claims are to methods of treating an hepatocarcinoma and of inducing apoptosis of a hepatocarcinoma cell comprising contacting a cell with an agent that inhibits cellular glutamine uptake by inhibiting ATB0 activity, and wherein the agent is a polynucleotide consisting essentially of SEQ ID NO: 3.

Bode, *et al.* teach inhibition of ATB0 activity in cells and in a patient as described above under the 102(b) and 103(a) rejections. Bode, *et al.* does not teach inhibition of ATB0 activity with a polynucleotide consisting essentially of SEQ ID NO: 3.

Khvorova, *et al.* teach the use of siRNAs for inhibiting gene expression via RNA interference (RNAi). They specifically teach SEQ ID NO: 461989, which is the same as the instant SEQ ID NO: 3 as shown.

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SEQ ID NO: 3 5'-aggaggtgctcgattcggtt-3'
              |||||
Khvorova, et al. SEQ ID NO: 461989 5'-aggaggugcucgauucguu-3'
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Art Unit: 1635

Khvorova, *et al.* teach that the siRNAs of their invention can be introduced into cells through vectors such as adenovirus vectors (p. 19, ¶ [0277]) and that the siRNAs can be used as therapeutics (*i.e.* in a patient) (p.1, ¶ [0009]).

It would have been obvious to perform the method of inhibiting ATB0 activity in a hepatocarcinoma cell as taught by Bode, *et al.*, with the nucleotide SEQ ID NO: 3 because Khvorova, *et al.* teach the use of SEQ ID NO: 461989 or a vector comprising SEQ ID NO: 461989 to inhibit gene (ATB0) expression in cells and in a patient (therapy). One would reasonably expect success in using the nucleotide for ATB0 gene inhibition because Khvorova, *et al.* teach that the siRNAs of their invention are useful as therapeutic agents against disease. Thus, claims 12, 14, 17, 19, and 29 would have been obvious to one skilled in the art at the time of the instant application.

Response to arguments

Applicant argues that because neither the Bode reference nor the Khvorova reference teaches or suggests apoptosis, that therefore a *prima facie* case of obviousness has not been established. This is not persuasive because the Bode, *et al.* teach the claimed steps and Khvorova, *et al.* teach the precisely claimed siRNA sequence and suggest administration for the treatment of disease. The induction of apoptosis is inherent in the claimed steps, absent evidence to the contrary as described in the above arguments.

Claim Rejections - 35 USC § 103 - new

Claims 1-7, 9, 10, 15, 20, 21, 22, 24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bode, *et al.* (1998, Surgery, v.124:260-8, of record) (Bode 1) as applied to

Art Unit: 1635

claims 1-6 and 24 above, and further in view of Bode, et al. (2002, Am J. Physiol. Gastrointest. Liver Physiol., v.283:G1062-73) (Bode 2), Bass (2001, Nature, v.411:428-9), Elbashir, *et al.* (2001, Nature, v.411:494-8) (Elbashir 1), and Elbashir, *et al.* (2001, EMBO J., v.20:6877-88) (Elbashir 2).

The claims are to methods of inducing apoptosis, comprising contacting a hepatocarcinoma cell *in vitro* or *in vivo* with an inhibitor of ATB0 expression, wherein the inhibitor is an siRNA.

Bode 1 teaches the inhibition of ATB0 by contacting SK-Hep cells with an ATB0 inhibitor as described above in the 35 USC § 102(b) rejection. Bode 1 does not teach a method wherein the contacted cells are in a patient and Bode 1 does not teach the method of inhibiting ATB0 with a polynucleotide or siRNA.

Bode 1 suggests the use of ATB0 inhibitors in patients as described previously. Bode 2 teaches that the mRNA sequence of ATB0 was known (p.G1062, second paragraph and p.G1063 last paragraph) and suggests that targeted molecular inhibition of ATB0 expression will provide further insights into the role of ATB0 in hepatoma cell growth and survival (p.G1072, last paragraph).

It was well known at the time of filing of the instant application that siRNAs were extremely useful for "knocking down" gene expression by RNA interference (RNAi). Bass teaches that RNA interference, mediated by double-stranded small interfering RNAs (siRNAs), was very well-recognized as a very useful tool for studying gene function once the sequence of a gene is known, that RNAi was accessible to all scientists, and that RNAi is now routine in laboratories (p.428, first paragraph). Elbashir 1 teaches that siRNA duplexes provide a new tool

Art Unit: 1635

for studying gene function in mammalian cells, and that siRNAs may eventually be used as gene-specific therapeutics (abstract and last paragraph).

Elbashir 2 also teaches that already in 2001, RNAi had rapidly developed into an important tool for reverse genetics and had been shown to be useful in mammalian cells if the siRNAs are less than 30 base-pairs in length (p.6878, second paragraph). They report their systematic analysis of length, overhangs, and sequence determinants of siRNA function. They conclude their report with guidelines for designing efficient siRNAs for inhibiting target gene expression (p.6855, “The siRNA user guide”). Elbashir, *et al.* describe efficient siRNAs as those duplexes composed of 21-nt sense and 21-nt antisense RNAs that form a 19-bp double helix with 2-nt 3'-overhanging ends. The authors further explain that target recognition is highly sequence-specific and is mediated by the siRNA complementary to the target, the 3'-most nucleotide of the guide siRNA does not contribute to the specificity of target recognition, while the penultimate nucleotide of the 3'-overhang affects target RNA cleavage and a mismatch reduces RNAi 2- to 4-fold, and that the 5'-end of the guide siRNA can have more mismatches to the target RNA when compared with the 3'-end. The authors further explain that nucleotides in the center of the siRNA are important for siRNA specificity determinants, the relative orientation of the siRNA duplex in the endonuclease complex determines the strand that can be used for target recognition, and give recommendations for the types and sequences of the 3'-overhanging sequences to ensure that the desired siRNA strand is the mRNA targeting strand. The authors describe that asymmetry in the siRNA-endonuclease complex or the target site sequence or accessibility of the target RNA may cause variation in efficiency of siRNA activity. Elbashir, *et al.* clearly demonstrate variation in siRNA efficiency for target inhibition and set forth guidelines

Art Unit: 1635

for the design of siRNAs. On page 6886, in their concluding remarks, Elbashir, *et al.* indicate that their results are important for the design of efficient siRNAs for silencing genes in *Drosophila melanogaster* and they provide a basis for similar studies in other organisms.

It would have been obvious to one of skill in the art at the time of filing of the instant application to make use siRNAs to inhibit ATB0 expression in hepatocarcinoma cells *in vitro* and *in vivo*. Bode 1 and Bode 2 teach that the ATB0 mRNA sequence was known and studies of inhibiting ATB0 in hepatocarcinoma cells had already been done. Bode 2 explicitly suggests targeted molecular inhibition of ATB0. Bode 1 suggests that better understanding of ATB0 may be used for the development of new therapies for hepatocarcinoma. Thus, these teachings indicate that further research on ATB0 was warranted and that ATB0 may be a good target gene for hepatocarcinoma therapeutics. Because both Bass and Elbashir *et al.* teach the ubiquitous use within the scientific community of siRNAs for interfering with gene expression, one of skill in the art would immediately recognize siRNAs as an easy and routine way to inhibit ATB0 gene expression for *in vitro* studies of the gene. Furthermore, Elbashir 1 presents siRNAs as potential gene-specific therapeutics. One of skill would recognize that siRNAs to ATB0 could serve as a potential cancer therapeutic in light of the teachings of Bode 1 and Bode 2. Bass, Elbashir 1, and Elbashir 2 also make it clear that production of any siRNA sequence would be a matter of routine experimentation and optimization, as Elbashir 2 set forth siRNA design guidelines. Therefore, one of skill in the art would recognize that siRNAs targeting ATB0 could be used as an inhibitor of ATB0 in place of the inhibitors taught by Bode, *et al.* Bode, *et al.* provide a reason to inhibit ATB0 for the treatment of hepatocarcinoma, which, as described above, is considered to inherently induce apoptosis, and Bass and Elbashir, *et al.* teach the routine and

Art Unit: 1635

robust nature of siRNAs for silencing target gene expression. Thus, the instant claims would have been obvious to one skilled in the art at the time of filing of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Pitrak whose telephone number is (571)270-3061. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1635

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Pitrak/
Examiner, Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635